## NON-SCIENTIFIC ABSTRACT

Over 50,000 new cases of bladder cancer are diagnosed annually in the United States, and 10,000 patients die yearly from the disease. Treatment of bladder cancer attempts to destroy or control the disease by preventing its progression to invasive, or widespread disease. Standard treatment includes surgical removal of tumors by a process called transurethral endoscopic resection (TURBT). Approximately half of patients that have TURBT treatment develop tumors again. These tumors can again be removed by TURBT. Chemotherapy and biological agents such as Bacillus Calmette-Guerin (BCG) are an important additional treatments that are often used along with TURBT. While chemotherapy and/or BCG are usually well tolerated, there are some patients who fail chemotherapy and/or BCG. In approximately 10% of patients, tumor recurrence is associated with their cancer invading into the muscle layer and beyond. If this happens standard treatment includes surgical removal of the bladder and surrounding tissues often combined with chemotherapy and/or radiation therapy. Despite aggressive treatment programs, approximately one half of patients with invasive tumors die of bladder cancer within 5 years.

The human retinoblastoma (RB) gene is called a tumor suppressor gene because it is believed to prevent normal cells from developing into cancer cells. When both copies of the RB gene become altered (such as by loss or mutation), cancers may form. Mutation or loss of expression of the RB gene product is linked to the uncontrolled growth of many types of human cancers and can occur as an early or later genetic event in the development of bladder cancer. RB alteration occurs in approximately 10-50% of patients with superficial bladder cancers, and also occurs in 30-80% of invasive bladder cancers. Bladder cancers with RB-alterations are associated with particularly poor prognosis. In scientific experiments using cells in the test tube and also in animals, introducing a normal copy of the RB gene into cancer cells that have abnormal RB can cause the cancer cells to grow more slowly, or stop growing.

ACNRB is a new gene therapeutic that contains the RB gene in a modified virus. The virus is used to deliver the gene into malignant tumor cells that have RB alterations. The modified virus has been constructed from an adenovirus most frequently associated with the common cold. The virus has been modified so that some parts of the virus necessary to reproduce itself have been deleted and in turn are replaced by the RB gene. The purpose of the study is to determine if the use of ACNRB in patients is safe. The study will also collect information to see if the reintroduction of the normal RB gene into malignant bladder tumors that are RB-altered can cause the tumors to grow more slowly, or stop growing. ACNRB will be given to patients with superficial and non-muscle invasive bladder cancer by a single administration directly into the bladder. The clinical trial will study the safety and effect of different doses of ACNRB using this new therapy. The maximum number of patients expected to be involved in this study is 24. Only those patients who have evidence of abnormal RB in their bladder tumor cells can enroll in the study, thereby selecting those patients who are the best candidates to benefit from this gene replacement therapy.